



UNITED STATES PATENT AND TRADEMARK OFFICE

8
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,618	10/23/2003	Jon Wulff Petersen	4528-0114P	5915
2292	7590	11/21/2007	EXAMINER	
BIRCH STEWART KOLASCH & BIRCH			OLSEN, KAJ K	
PO BOX 747				
FALLS CHURCH, VA 22040-0747			ART UNIT	PAPER NUMBER
			1795	
			NOTIFICATION DATE	DELIVERY MODE
			11/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)
	10/690,618	PETERSEN ET AL.
	Examiner	Art Unit
	Kaj K. Olsen	1795

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 07 September 2007.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-30 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date, _____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-15 and 17-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/31503 (hereafter “WO ‘503”) in view of Nisch et al (USP 6,315,940), Rubinsky et al (USP 6,300,108) or Kostyuk et al (Nature, 257, pp. 691-693, October 1975).

4. WO ‘503 discloses an assembly comprising a plane substrate 1 having a plurality of sites adapted to hold an ion-channel containing structure (i.e. a cell) each of which have a passage 3 dimensioned to hold the ion-channel containing structure and form a high resistance seal between the ion-channel containing structure and the substrate along the passage. See fig. 3 and p. 12, ll. 12-27 for a discussion of the individual sites and claim 11 for a discussion of the plurality of sites. WO ‘503 further discloses a plurality of measuring electrodes 9 and reference

electrodes 6 each associated with each respective site. Each of the sites is adapted to provide a high electrical resistance seal between an area of contact with an outer surface of an ion channel containing structure and the first surface part of the substrate whereby a current flowing between the reference and measuring electrodes and through the ion channel containing structure can be determined and monitored. See p. 12, ll. 12-27 and p. 15, l. 15 through p. 16, l. 4. Figures 3 and 4 of WO '503 also show the electrodes being integrated with the assembly. WO '503 does not explicitly recite the presence of a plurality of flow channels created in the substrate for delivering liquids to the sites. However, WO '503 does suggest that the compartments of its substrate can be connected to conventional flow systems for delivering fluids to the various compartments.

Nisch, Rubinsky, and Kostyuk all teach how to integrate flow channels to electrophysiological substrates. In particular, Nisch teaches the presence of flow channels 23 etched into the substrate to provide fluid and electrical contact for the cells. See fig. 1A, 1B and col. 6, l. 64 through col. 7, l. 20. Rubinsky also teaches the presence of channels (13 and the inlet and outlet for 13) for delivering needed fluid to the lower compartment and cell to be treated. See fig. 1 and 2 and col. 6, ll. 49-65. Kostyuk also discloses the use of a flow channel beneath an electrophysiological site for controlling fluid content for the voltage clamping experiment. See fig. 1. It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teaching of any of Nisch, Rubinsky, or Kostyuk for the device of WO '503 so as to conveniently interface fluid inlet and outlet to the lower compartments of cell assays.

5. With respect to the plane substrate also having a first side and second side, WO '503 discloses the use of spacers 12 which would define a first side with the opposite side of substrate 1 reading on the defined second side of the claims. See fig. 3 and compare with marked up fig.

4A provided by the applicant's on 9-7-2007. The second substrate thickness (equivalent to the thickness of element 1) is less than the thickness defined by elements 1 and 12 of WO '503.

6. WO '503 further discloses a first substrate component (10 and/or 12) and a second substrate component (1 and/or 10) where the first and second substrate components inherently have first and second faces where the face of one of the components is attached to the face of the other component. See fig. 3 of WO '503.

7. With respect to the silicon/silica substrate, see p. 12, ll. 22 and 23 of WO '503.

8. With respect to the presence of at least 9 sites, WO '503 didn't explicitly disclose a number of sites. However, it would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize at least 9 sites such that a large number of parallel ion channel analyses could be performed at the same time for greater information throughput. In addition, Nisch discloses the use of at least 9 measuring sites as well. See fig. 4.

9. With respect to the use of silver/silver halide electrodes. See WO '503, p. 20, ll. 18-22. See also Kostyuk, p. 692, where Ag/AgCl electrodes are utilized for both the measuring and reference electrodes.

10. With respect to the hydrophobic material, see p. 13, ll. 19-21.

11. With respect to the use of funnel shaped wells, see fig. 1 and 3 and p. 21, l. 4 of WO '503. See also Nisch, fig. 3, 5, and 6.

12. With respect to the process that the wells are to be formed, the determination of patentability for the claim is based on the product itself. Because the product of the claim is identical to the invention of WO '503 in view of Nisch, Rubinsky, or Kostyuk, the process from

which it was made is the same as or obvious over the process utilized by WO '503 in view of Nisch, Rubinsky, or Kostyuk (see *In re Thorpe*, 777 F.2d 695, 698).

13. With respect to the reference electrode being positioned on a side surface of the well, electrode 9 of fig. 3 of WO '503 is along a side surface of the well. With respect to this electrode being a reference electrode, the term "reference electrode" merely identifies how one intends to utilize said electrode and doesn't further define any inherent structure for the electrode (especially when applicant utilizes Ag/AgCl for both the measuring and reference electrodes).

Hence, electrode 9 of fig. 3 would read on the defined reference electrode.

14. With respect to the generation of an amplified signal, fig. 1 of Kostyuk shows a high gain amplifier connected to the measuring electrodes.

15. With respect to the specified mean for connecting, both Rubinsky (col. 12, l. 49 through col. 13, l. 5) and Kostyuk (p. 692) teach the use of pressure differentials for creating a suction.

16. With respect to the method claims (those limitations not covered above), WO '503 also measures the resistance of its voltage clamps (p. 28, ll. 5-12), which WO '503 earlier disclosed is arrived at by a measurement of voltage and current and an application of Ohm's law. See p. 15, ll. 8-14. Hence, WO '503 already discloses applying a first electric potential difference and monitoring a first current flow in order to measure the strength of the electric seal. With respect to this applied potential difference being successive, fig. 9 shows a continuous (i.e. successive) monitoring of current until a suitable current level is measured. See the description of fig. 9 on p. 11. With respect to comparing this first current to a predetermined threshold current, because WO '503 already recognized what it deemed to be acceptable levels of current leakage (p. 15, ll. 15-19), one possessing ordinary skill in the art would have been motivated to only deem a seal to

be acceptable provided it arrives a first current that is below or at a predetermined threshold current (as fig. 9 appears to be indicating). With respect to measuring a third current, once the seal of WO '503 is established, WO '503 shows in fig. 12 the analysis that proceeds. See the description of fig. 12 on p. 11.

17. With respect to the pore former, see WO '503, p. 23, ll. 5-9.
18. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO '503 in view of any of Nisch, Rubinsky, or Kostyuk as set forth for claim 15 above, and in further view of Knoll et al (USP 5,393,401).
19. The references set forth all the limitations of the claim, but does not explicitly identify the use of a 54.7° slope for the well openings (although fig. 1 of WO '503 appears to be substantially close to 54.7°). However, Knoll teaches that said angle is the conventional result of an anisotropic etching of a single crystal Si wafer. Said angle provides a continuous (111) crystal plane thereby improving the stability of the wafer surface (col. 2, line 60 though col. 3, line 8). It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teaching of Knoll for the device of WO '503 in order to provide stable crystal surfaces along the etched out substrate well.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,682,649 in view of any of Nisch, Rubinsky, or Kostyuk.

22. The claims of the instant invention substantially overlap the claims of the patent. In particular, claim 1 of the patent appears to substantially comprise limitations from claims 1, 15, and 23 of the instant invention. Claim 24 of the patent appears to substantially comprise limitations 24 and 23 of the instant invention. Hence, most of claims 1 and 24 of the instant invention fully encompass the claims of the patent. Although the claims of the patent do not explicitly recite the presence of flow channels, the various teachings of Nisch, Rubinsky, and Kostyuk all rendered obvious the addition of flow channels to the substrate for the delivery of fluid to the measurement sites (see detailed discussion above). It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize the teachings of any of Nisch, Rubinsky, or Kostyuk for the claimed invention of the patent so that fluid can be easily delivered to the measurement sites. With respect to the various dependent claims of the instant invention, these limitations all appear to have claim limitations in the patent and also fully encompass the claims of the patent.

Response to Arguments

23. Applicant's arguments filed 9-7-2007 have been fully considered but they are not persuasive. Applicant principally traversed the outstanding rejections by addressing each of the teachings of Nisch, Rubinsky, and Kostyuk and the applicant's belief in the failings of each of these teachings in rendering obvious the claimed invention. The examiner will address each of these references and their arguments separately.
24. With respect to the teaching of Nisch, applicant opens with a comment that the instant invention as claimed is drawn to an ion-channel containing structure that may be positioned at a site using an electrical field to generate an electroosmotic flow in a canal. The examiner would note that the claimed invention does not appear to require anything concerning the use of electroosmotic flow in a canal and this point is moot. Applicant further urges that Nisch does not relate to the technical field of patch clamping as evidenced by col. 2, ll. 49-54. First, the examiner believes this is inaccurate because this passage is referring to the process of traditional patch clamping that utilized pipettes. Because Nisch did not rely on pipettes, it considers such a technique to be different from its disclosure. This is no different than the teaching of WO '503, which considered patch clamping based on pipettes as being a different technique as well. See the third paragraph of p. 4. See also col. 2, ll. 60-67 of Nisch, which makes it clear that the difference between the teaching of Nisch and "patch clamping" is merely the limitations on performing multiple analyses with multiple pipettes. Furthermore, Nisch is drawn to devices for stimulating and sensing processes involving cells or artificial vesicles with incorporated pores therein. See col. 1, ll. 23-34. This is analogous to WO '503, which is a technique for stimulating

and sensing cells or vesicles containing pore channels. See “Technical Area” on p. 3 of WO ‘503. Moreover, Nisch is drawn to the general concept of making “it possible to bring individual cells in controlled fashion from a liquid environment into contact with the microelements and to make good contact there” (col. 2, ll. 8-11. This is precisely relevant to WO ‘503, which requires cells or vesicles to be placed into contact with a micro-aperture to ensure a good electrical seal (i.e. a gigaohm seal). See WO ‘503, final paragraph of p. 27.

25. Applicant also urges that the electrodes of Nisch are both in the same domain as the biological sample and hence there would be no way of measuring a current flowing between the measuring and reference electrodes. However, WO ‘503 already established that the measurement and reference electrodes are to be placed on opposite sides of the aperture. Nisch is only being relied on for its teaching of placing flow channels beneath an electrophysiological device so as to facilitate the cell movement and provide the necessary assay fluid. Applicant further urges that Nisch uses its common channel by applying a negative pressure to cause the cells to be aspirated onto the electrodes and that this reads free of the teaching of Nisch. The examiner disagrees. Common channel 23 combined with stub channels 22 read on the defined “plurality of flow channel structures” and they deliver fluid to the various sites by the pulling fluid from the microcuvettes towards the measurement site. Hence, the channels are “for delivering liquid to said plurality of sites” giving the claim language its broadest reasonable interpretation, even though the channels themselves are not actually carrying the fluid. The channels are not required to carry the fluid in the claims, only that they supply or deliver the liquid, which the channels of Nisch do.

26. With respect to the teaching of Rubinsky, applicant urges that it is drawn to the fields of electroporation and mass transfer across cells. First, it is unclear why applicant deems this to be in conflict with WO '503 as the patch clamp analysis utilized by WO '503 is often performed on cells that have been treated by electroporation. Second, Rubinsky is being utilized solely for its teaching that flow channels incorporated into the substrate can be utilized for the delivery of the materials, including the cells themselves, to the measurement site. See col. 5, ll. 44-52.

Moreover, Rubinsky is structurally very analogous to the teaching of WO '503. In particular, Rubinsky delivers cells along a flow channel to an aperture that separates two electrodes from each other, which is exactly what WO '503 is doing as well. Compare fig. 2 of Rubinsky to fig. 3 of WO '503. Note also that WO '503 already disclosed that flow channels in the form of pipettes or tubes would be necessary for delivering the sample to the measurement sites (p. 21, third paragraph). WO '503 just didn't teach that those flow channels would be "in the substrate" as required by the claims. Rubinsky teaches that flow channels providing the same function as the pipette or tubes of WO '503 can be incorporated into the substrate itself. One possessing ordinary skill in the cell assay art would recognize that this flow channel teaching of Rubinsky would have utility for any number of technologies drawn to cell delivery, manipulation, and analysis, including the delivery and analysis of WO '503. Applicant further urges that because channel 13 is carved out to define lateral boundaries of the lower liquid chamber, it is not suitable for delivering liquid to the plurality of sites. This argument is not understood. Isn't piping 32 of the instant invention essentially carved out of the lower substrate? Would any flow channels created in the upper substrate by normal etching (see specification p. 16, ll. 29-33) be carved out as well? If the applicant is alluding to the fact that Rubinsky doesn't teach flow

Art Unit: 1795

channels that would deliver to a plurality of sites, Rubinsky teaches the use of a given flow channel for a given cell manipulating site. Because WO '503 already set forth the use of a plurality of cell manipulating sites (see claim 11), that thereby renders obvious the provision of a plurality of flow channels for delivering fluid to a plurality of sites.

27. With respect to the teaching of Kostyuk, applicant urges that Kostyuk is not related to patch clamping as well. First, the examiner does not believe this is accurate as Kostyuk identifies itself as being a "voltage clamp technique" (p. 691) and the examiner believes said term is synonymous with the term "patch clamp". In particular, Kostyuk is placing a cell over a small aperture (i.e. pore) and monitoring the current and voltage across the cell membrane. See p. 692. This is precisely analogous to what WO '503 is also doing. Second, even if the experiment that Kostyuk is performing wouldn't meet the explicit meaning of the term "patch clamp", the main reason the examiner is relying on the teaching of Kostyuk for is that flow channels can be utilized for controlling fluid movement and cell position for a cellular assay. In particular, Kostyuk discloses a flow channel below the measurement site for manipulating the cell to the pore and appears to show flow channels in the upper compartment as well (see the holes and arrows in the upper compartment of fig. 1). This is precisely relevant to the teaching of WO '503 even if the ultimate analyses of Kostyuk and WO '503 differ. With respect to whether Kostyuk would be appropriate for delivering fluid to a plurality of sites, Kostyuk teaches the use of a given flow channel for a given cell analysis site. Because WO '503 already set forth the use of a plurality of cell manipulating sites (see claim 11), that thereby renders obvious the provision of a plurality of flow channels for delivering fluid to a plurality of sites.

28. Applicant urges that the examiner must identify a reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. The examiner believes that he has already done so. See paragraph 12 from the previous office action (also reprinted above). In the absence of specific arguments as to how the examiner has erred, the examiner believes the burden of *prima facie* obviousness has been met.
29. Applicant's traversal of the rejection of the method claims and the dependent claims appear to rely on the applicant's perceived failings of the earlier discussed teachings. Similarly, applicant's traversal of the double patenting rejection also appears to hinge on the perceived failings of these teachings. However, those arguments were not persuasive as discussed above and these rejections are also being maintained.

Conclusion

30. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 1795

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kaj Olsen whose telephone number is (571) 272-1344. The examiner can normally be reached on Monday through Friday from 8:00 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen, can be reached on 571-272-1342. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AU 1795
November 15, 2007



KAJ K. OLSEN
PRIMARY EXAMINER